NDA 50-456

S-020

NDA 50-456/S-020

Alcon Laboratories
Attention: Cheryl B. Anderson, Pharm. D.
Regulatory Affairs Manager
6201 South Freeway
Fort Worth, TX 76134

Dear Dr. Anderson:

Please refer to your supplemental new drug application dated March 7, 1997, received March 17, 1997, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for STATROL® (neomycin and polymyxin B sulfates ophthalmic solution, USP) Opthalmic Solution.

We acknowledge receipt of your submissions dated March 18 and July 29, 1997.

This supplemental application provides for the addition of a Pediatric Use subsection in the Precautions section of the package insert.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated July 29, 1997, with the revision listed below. Accordingly, the supplemental application is approved effective on the date of this letter. As discussed by telephone on August 6, 1997, between Ms. Susan Caballa and Ms. Joanne Holmes of this Division, the following revision will be made:

> "Sulfate" will be revised to "sulfate" in the second paragraph of the Carcinogenesis subsection of the Precautions section.

This revision is a term of the supplemental NDA approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 50-456/S-020. Approval of this submission of FPL by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

This approval affects only the changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

If you have any questions, please contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

WAC 9/9/97
Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
NDA 50-456
HFD-550/Div. files
HFD-105/ODE 5
HFD-550/Dep Dir/Chambers (with labeling)
HFD-550/MO/Bull (with labeling)
HFD-550/Clin Rev/Holmes (with labeling)
HFD-550/Proj Mgr/Gunter (with labeling)
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)

Drafted by: jh/August 6, 1997/50456s20.ap

APPROVAL (AP)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

DRAFT LABELING IS **NO LONGER** BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

Clinical Review of NDA
Labeling Supplement 50-456

MAY 27 1997

NDA 50-456/S-020

Submission Dates: 3/7/97
3/18/97
7/29/97

Review Date: 5/27/97

Applicant: Alcon Laboratories
6201 South Freeway
Fort Worth, TX 76134

Applicant's Representative: Cheryl B. Anderson, Pharm. D.
Regulatory Affairs Manager

Drug: STATROL® (neomycin and polymyxin B sulfates ophthalmic solution, USP)

Pharmacologic Category: Combination anti-infective

Submitted: Revised draft labeling of the package insert to add a Pediatric Use subsection. The 3/7/97 submission contains 2 versions: a copy of FPL from June 1995, with the Pediatric Use subsection typed in; the other is February 1997 revised draft. There were differences between the two. On 5/28/97, Alcon was asked to amend the supplement to clean up the errors and to propose an age limit in the Pediatric Use subsection. The 7/29/97 submission addresses these. (The 3/18/97 submission is a User Fee cover sheet.)

Following is the labeling submitted by the company. Reviewer recommended deletions are noted by ~~strikeout~~ and additions by shading within the review.

Statrol®
neomycin and polymyxin B sulfates ophthalmic solution, USP

DESCRIPTION: STATROL® (neomycin and polymyxin B sulfates ophthalmic solution, USP) is a sterile ophthalmic drug combining two antibacterials in solution form.

Each mL of solution contains: Active: Neomycin Sulfate equivalent to 3.5 mg Neomycin base, Polymyxin B Sulfate equal to 16,250 polymyxin B units. Preservative: Benzalkonium Chloride 0.004%. Vehicle: 0.5% Hydroxypropyl Methylcellulose 2910. Inactive: Boric Acid, Sodium Chloride, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), Purified Water.

Reviewer's comments: *The generic name has been revised to appear in lower case letters, as neomycin and polymyxin B sulfates ophthalmic ointment, USP.*

CLINICAL PHARMACOLOGY: The anti-infective components in STATROL Ophthalmic Solution provide action against specific organisms susceptible to them. Polymyxin B sulfate and neomycin sulfate are active *in vitro* against *Staphylococcus aureus, Escherichia coli, Klebsiella/Enterobacter* species, *Neisseria* species, *Pseudomonas aeruginosa.* This product does not provide adequate coverage against: *Serratia marcescens,* Streptococci, including *Streptococcus pneumoniae.*

Reviewer's comments: *Capitalization errors of Neisseria, polymyxin B, and neomycin sulfate have been corrected throughout the text (with one exception, noted later).*

INDICATIONS AND USAGE: STATROL Ophthalmic Solution is indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections encompass conjunctivitis, keratitis and keratoconjunctivitis, blepharitis and blepharoconjunctivitis, acute meibomianitis and dacryocystitis.

CONTRAINDICATIONS: Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of ocular structures. Hypersensitivity to a component of the medication.

WARNINGS: NOT FOR INJECTION INTO THE EYE. Should a sensitivity reaction occur, discontinue use. Ophthalmic Solutions may retard corneal wound healing. Neomycin sulfate may cause cutaneous sensitization. Remove contact lenses before using.

PRECAUTIONS: General: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms including fungi. If superinfection occurs, appropriate measures should be initiated. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, corneal staining.

Information for Patients: This product is sterile when packaged. To prevent contamination, care should be taken to avoid touching the bottle tip to eyelids or to any other surface. The use of this bottle by more than one person may spread infection. Keep bottle tightly closed when not in use. Keep out of the reach of children.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic or mutagenic potential have not been conducted with polymyxin B sulfate. Treatment of cultured human lymphocytes *in vitro* with neomycin increased the frequency of chromosome aberrations at the highest concentrations (80 µg/mL) tested; however, the effects of neomycin on carcinogenesis and mutagenesis in humans are unknown.

Polymyxin B ~~S~~sulfate has been reported to impair the motility of equine sperm, but its effects on male or female fertility are unknown.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Animal reproduction studies have not been conducted with STATROL® (neomycin and polymyxin B sulfates ophthalmic solution, USP). It is also not known whether neomycin sulfate and/or polymyxin B sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. STATROL Ophthalmic Solution should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether these drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when STATROL Ophthalmic Solution is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Reviewer's comments: *Various typographical errors in the Precautions section have been corrected, although one occurrence of capitalizing polymyxin B sulfate, in the second paragraph of the Carcinogenesis subsection, was overlooked. The Pediatric Use subsection was added in this supplement, is supported by literature references, and was revised in the 7/29/97 submission to allow for a lower age limit. Acceptable.*

ADVERSE REACTIONS: Adverse reactions have occurred with the anti-infective components. Exact incidence figures are not available since no denominator of treated patients is available. Reactions occurring most often from the presence of the anti-infective ingredients are allergic sensitizations. (SEE WARNINGS.)

DOSAGE AND ADMINISTRATION: Instill one or two drops in the lower conjunctival sac(s) three or more times daily as required.

HOW SUPPLIED: STATROL (neomycin and polymyxin B sulfates ophthalmic solution, USP) in 5 mL plastic DROP-TAINER® dispenser: NDC 0998-0623-05.

STORAGE: Store at 46° - 80°F (8° - 27°C).

Federal (USA) law prohibits dispensing without prescription.

Alcon®
OPHTHALMIC
ALCON (Puerto Rico) INC.
Humacao, Puerto Rico 00791 USA

Revised July 1997
Printed in USA

Recommendation: The revised labeling is acceptable as proposed and an approval letter requesting FPL may be issued. Susan Caballa of Alcon agreed to the following change in a telephone conversation on August 6, 1997: "Sulfate" will be revised to "sulfate" in the second paragraph of the Carcinogenesis subsection of the Precautions section.

Joanne M. Holmes

Wiley A. Chambers, M.D.

cc:
NDA 50-456
HFD-550/Div. files
HFD-550/MO/Bull
HFD-550/Dep Dir/Chambers
HFD-550/Clin Rev/Holmes
HFD-550/Proj Mgr/Gunter
HF-2/MedWatch

DUPLICATE

CENTER FOR DRUG
REC'D
MAR 17 1997
MEGA DOC ROOM

Certified Mail Z 047 936 569
Return Receipt Requested

March 7, 1997

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager

Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA NO. 50456 REF. NO. S-020
SUPPL FOR Draft

RE: NDA 50-456
STATROL® SOLUTION
Neomycin and Polymyxin B Sulfates
Supplemental Application

Dear Madam or Sir:

The December 13, 1994 Federal Register published the Final Rule: "Specific Requirements on Content and Format of the Labeling for Human Prescription Drugs; Revisions of "Pediatric Use" Subsection in the Labeling." The notice requested that sponsors reexamine existing data and, if appropriate, submit a supplemental application to comply with the current 201.57(f)(9).

In accordance with the final rule, this supplemental application proposes the addition of a Pediatric Use section to the labeling. Four copies of draft labeling are provided.

If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm. D.

CBA/ple

Enclosures

REVIEWS COMPLETED 4/14/97
CDC ACTION:
☐ LETTER ☐ FAX ☐ E-MAIL
CSO INITIALS DATE

ORIGINAL

Certified Mail Z 047 936 583
Return Receipt Requested

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager

March 18, 1997

Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

ENC 020
SUPPL NEW CORRESP

RE: NDA 50-456
STATROL® SOLUTION
(neomycin and polymyxin B sulfates)
Supplemental Application

Dear Madam or Sir:

On March 7, 1997, a supplemental application to add a Pediatric Use subsection to the package insert was submitted. The User Fee Cover Sheet was inadvertently omitted. Following you will find the necessary form.

If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm. D.
Manager Regulatory Affairs

CBA/ple

Enclosures

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

AirBorne Express 2204147960
c/o Booze Messenger Service

July 29, 1997

NDA SUPPL AMEND

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm.D.
Regulatory Affairs Manager

Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
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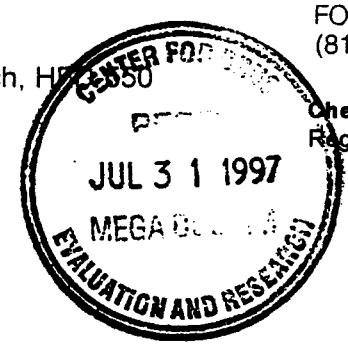
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850



RE: NDA 50-344
STATROL® OINTMENT
(neomycin and polymyxin B sulfates ophthalmic ointment)

NDA 50-456
STATROL® SOLUTION
(neomycin and polymyxin B sulfates ophthalmic solution)
Amendment to Pending Application

Dear Madam or Sir:

A supplemental application was filed on March 7, 1997 in response to the December 13, 1994 Federal Register published the Final Rule: "Specific Requirements on Content and Format of the Labeling for Human Prescription Drugs; Revisions of "Pediatric Use" Subsection in the Labeling." The notice requested that sponsors reexamine existing data and, if appropriate, submit a supplemental application to comply with the current 201.57(f)(9).

This amendment revises our original submission per FDA request. As requested, the pediatric use section has been revised to: "Pediatric Use: Safey and effectiveness in pediatric patients below the age of 2 years have not been established." The supporting data is provided in this amendment. Four copies of draft labeling are provided.

If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

Cheryl Beal Anderson, Pharm.D.

Desk Copy: Joanne Holmes, Project Manager